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EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,228	STOFFELS, PAUL	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *2,4,5,9-18 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 6-8 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/28/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending and are subject of this office action.

Claims 2, 4-5, 9-18 and 24 are withdrawn from consideration as being drawn towards a nonelected invention.

Claims 1, 3, 6-8 and 19-23 are under consideration in the instant office action.

Election/Restrictions

Applicant's election with traverse of Group II (claims 1, 3,6,7,8 and 19-23) in the reply filed on 09/18/2008 is acknowledged. The traversal is on the ground(s) that a search of for the combination of TMC278 with both a nucleoside and nucleotide reverse transcriptase inhibitor would not be an undue burden.

Examiner finds the applicant's argument unpersuasive and maintains the restriction since there is a search burden as the inventions are patentably distinct and independent. First, the different groups are not united by a special technical feature as detailed in the restriction requirement dated 08/19/2008. Secondly, the inventions are structurally divergent, differ in their physical, chemical and biological properties and activities and thereby require searching in different class/subclasses and use of different search queries.

Thereby the restriction requirement is still deemed proper and is therefore made FINAL.

Claims 2, 4-5, 9-18 and 24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 09/18/2008.

Claims 1, 3, 6-8 and 19-23 are under consideration in the instant office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description rejection:

Claims 1 and 3 and dependent claims 6-8 and 19-23 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set

forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims recites a genus of drugs that is defined only by the fact that they are a “prodrug” of TMC278. There is insufficient written description of the claimed prodrugs because Applicants have not described such prodrugs in a manner that would indicate they were in possession of these prodrugs of water soluble drugs at the time of the invention. For example, Applicants have not provided any examples of such prodrugs and have not described these prodrugs by providing structures or structural characteristics. Accordingly, Applicants have not demonstrated possession of the claimed prodrugs of water soluble drugs.

Although general synthetic techniques may be known in the art, this fact fails to diminish the amount of experimentation that the skilled artisan would have to undertake

to identify and synthesize, let alone determine the full scope of, the claimed prodrugs of water soluble drugs which are made hardly water soluble, particularly in view of the fact that this genus as a whole is not one that is well-known or well-defined in the art such that the skilled artisan would readily envision those compounds that are within the scope of the claimed genus.

"Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention." Please see MPEP § 2163.

Applicants are imposing the burden of extensive testing upon the skilled artisan to identify those prodrugs that may have any of the disclosed functions (NNRTIs), but which Applicants have not identified and thus, were not in possession of, at the time of the present invention.

It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicants may have a plan for how to identify prodrugs that may be amenable for use in the present invention, it remains that at the time of the invention;

Applicants had not identified such prodrugs, and, therefore, did not have written description of the full scope of the genus claimed.

Enablement rejection

Claim 23 which is drawn towards a combination as claimed is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling one of the uses of the combination as medicine which is for treatment of HIV 1, does not reasonably provide enablement for other different uses as medicine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. These is a scope of enablement rejection

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:
The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing Ex parte Forman, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance provided, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims..

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

(1) The nature of the invention: Claims 23 recites a combination as claimed for use as a medicine

(2) State of the prior art: The instantly claimed combination comprises of well known anti-HIV 1 which belong to broader classes of non nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleotide reverse transcriptase inhibitors (NRTI). Compounds belonging to both these classes are specifically used for the the treatment of AIDS and AIDS related conditions caused by HIV-1. Mechanism of action of these agents involves interaction with the HIV-1 reverse transcriptase enzyme. Accordingly, these agents will

not be useful in the treatment of any disorders and diseases which are not associated with the reverse transcriptase enzyme.

(3) The breadth of the claims: The claims are extremely broad in that they encompass use of the combination in medicine for treating several different disorders and conditions; it also encompasses use of medicines as a prophylactic and for preventive use in various disorders and conditions.

(5) The amount of direction or guidance provided and the presence or absence of working examples: In the instant case, working examples are provides demonstrating the activity of the instantly claimed combination for treatment of HIV-1 disease (page 23 of instant disclosure) and However, there are a lack of working examples presented in the specification as filed showing how to use this composition for use as a medicine for other different disorders and condition.. Note that lack of a working example is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP § 2164.

(6) The quantity of experimentation necessary: In the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept that the combination as claimed could be used in the treatment any type of diseases or conditions. Selection of the different conditions for which the combination can be used as a medicine would require screening the instantly claimed combination in assays

known to correlate with clinical efficacy of such disorders and conditions, determine routes of administration and formulation into a dosage form. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the inventions of claim 23 do not comply with the scope of enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

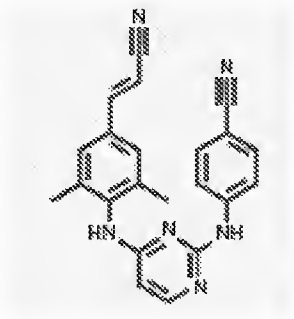
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 6-8 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guillemont (WO 03/016306, referenced in the instant IDS) as

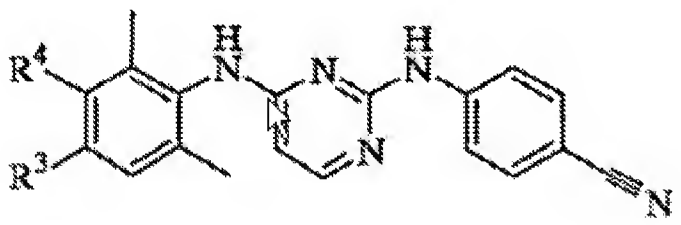
evidenced by Clercq (Il Farmaco 54 (1999) 26-45) in view of Peiperl et al (Viread, drug overview, August 2003).

Instant application claims a combination comprising TMC278 (NNRTI) or a stereoisomeric form thereof with a nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir.

TMC278 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with the following structure:



Guillemont teaches the E and the Z-isomeric forms of TMC278 as compounds 1 and 10 on pages 91 and 95 of the instant disclosure respectively (see below)



Comp No.	Ex. No.	R^3	R^4	Physical data mp.°C / (MH+)*
1	B1/B6a	-CH=CH-CN	H	mp. 245, (E)
10	B6a	-CH=CH-CN	H	mp. 258°C (Z)

Guillemont additionally discloses these compounds to display antiretroviral properties (page 43, lines 4-5) and as active against (multi) drug resistant HIV strains, especially HIV strains that have acquired resistance to one or more art-known non-nucleoside reverse transcriptase inhibitors (page 43, lines 2029). Guillemont additionally teaches that compounds of his invention may be used alone or in combination with other therapeutic agents such as anti-viral, antibiotics etc (page 51, lines 12-15). Guillemont also teaches that the exact doses and frequency of administration depends on the particular compound, the severity of condition being treated, the age, weight and general physical condition of the particular patient as well as other medications the individual may be taking and is well known to those skilled in the art (page 51, lines 1-6). Guillemont teaches that his compounds of his invention may be formulated into various pharmaceutical forms for administration purposes in combination with pharmaceutically acceptable carriers (page 44, lines 26-33). Guillemont additionally teaches that the combination of an antiretroviral compound and the compound of formula (I) (which encompasses compound 1 and 10 shown above) can be used in medicine. (Page 51, line 25 to page 52, line13). Guillemont exemplifies other NtRTI's such as tenofovir (page 52, line 12). Guillemont additionally teaches the that by administering compounds of his invention with other anti-viral agents which

target different events in the viral life-cycle, the therapeutic effect of these compounds can be potentiated and combination therapies exert synergistic effect , may reduce the dosage of a given conventional anti-retroviral agent, may reduce or eliminate the side effects of conventional single anti-retroviral therapy and may increase the efficacy of the conventional agent without increasing associated toxicity (page 52, lines 15-17).

Clercq is used here as evidentiary document to support the use of NNRTI and NtRTI drugs in HIV 1 therapy. Clercq teaches perspective of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the therapy of HIV-1 Infection (title). Clercq teaches that NNRTI resistance mutations is generally felt as compromising the clinical utility of the NNRTI's (page 29, right col. last paragraph to page 30 left col. 1st paragraph). Clercq further teaches that the mutually antagonistic effects of different resistance mutations and the hypersensitivity that is seen under some conditions argue in favor of the combined use of NNRTI's with NRTI (nucleoside/nucleotide reverse transcriptase inhibitors). Additionally, Clercq teaches that while achieving synergism in their anti-HIV action, different drugs combined may also reduce the risk of HIV drug resistance development and diminish toxic side effects. (Page 30, right col., 1st paragraph to page 31, right col., 1st paragraph). Clercq additionally teaches that the compound should be administered concomitantly (page 31, right col., 1st paragraph).

Guillemont does not teach the specific utility of tenofovir in HIV treatment and once a day dosing of the combination.

However, Peiperl teaches that tenofovir which is an adenosine nucleotide analogue was approved by the FDA in 2001 for use in combination with other

antiretroviral agents in adults with HIV infection (page 1, under approval). Peiperl teaches that tenofovir is available in tablet form with once daily dosing (page 1). Peiperl additionally teaches that tenofovir in combination wit lamivudine (nucleoside reverse transcriptase inhibitor) and efavirenz (non-nucleoside reverse transcriptase inhibitor) was found to be well tolerated and apparently more potent than the standard regimen (page 2, 1st paragraph) and in a clinical comparison this combination was associated with a lower rate of toxicities attributable to mitochondrial dysfunction (page 3, 1st paragraph).

With regards to the ratio limitation in instant claim 19 wherein the applicant claims a weight ratio of each couple of components to be in the range form 1/4 to 4/1 the references above do not teach the exact ratio in a combination of the NNRTI and NtRTI inhibitors. However, it would be within the skill of an ordinary artisan to be able to titrate the dosage of both compounds in a composition to obtain the desired pharmacological and pharmaceutical effects. The ratio also will depend on the dosage regiment if it is sequential or concomitant administration. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In view of the foregoing references, the instantly claimed combination comprising TMC278 and tenofovir would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made. Guillemont teaches both isoforms of TMC278 and suggest combination of that with Tenofovir for use as a medicine for HIV 1

treatment. Peiperl teaches tenofovir composition designed for once daily dosage in treatment of HIV 1. All three references provide one of ordinary skill in the art motivation to combine a non-nucleoside reverse transcriptase inhibitor (NNRTI) with a Nucleotide reverse transcriptase inhibitor (NtRTI) and the advantages of using them in combination. All of the materials instantly claimed were known in the art to be useful to obtain an efficient anti HIV-1 drug. Accordingly, the references above provide motivation to one of ordinary skill in the art to formulate a medicine comprising the combination of the compounds taught by Guillemont which includes the two isomeric forms of TMC278 and tenofovir for HIV 1 treatment. Moreover, both NNRTIs and NtRTIs are individually known in the art as agents for treating HIV-1 conditions as shown supra, whose efficacy when administered alone is well established. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In re Kerkhoven, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. In re Crockett, 126 U.S.P.Q. 186, 188 (CCPA 1960).Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed supra). The natural presumption that two individually known anti-HIV agents would, when combined, provide a third composition also useful for treating HIV flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (e.g. unexpected results) to rebut this natural presumption.

Further, it is clear from the prior art that NNRTI combination with other drugs such as NtRTIs provide several advantages such as synergistic effect , reduction in the dosage and reduction of side effects. One skilled in the art would have been imbued with at least a reasonable expectation that a combination of NNRTI with NtRTI would provide a composition with enhanced and beneficial effects.

Conclusion

Claims 1, 3, 6-8 and 19-23 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
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